REMARKS

Claims 11-14 and 19 are pending in the subject patent application, and all stand finally rejected. Claims 11 and 12 have been amended herein to recite "biologically active beta-secretase." No new matter is added by these amendments.

Rejection Under 35 USC, Section 112

Claims 11, 12, and 19 have been rejected under 35 USC, Section 112, second paragraph as allegedly indefinite in the use of the phrase "biologically active". Without conceding to the merits of this rejection, Applicants have amended claims 11 and 12 to recite "biologically active beta-secretase" per the Examiner's suggestion. Claim 19 has not been amended, as it depends from claim 11.

Applicants submit that in view of the amendments to claims 11 and 12 herein, this rejection has been overcome. As such, Applicants respectfully request reconsideration and removal of this rejection.

Rejection Under 35 USC, Section 102(e)

Claims 11-14 have been rejected under 35 USC, Section 102(e) as anticipated by Powell *et al.* (U.S. Patent No. 6,319,689 B1). According to the Examiner, Powell *et al.* disclose a polynucleotide that "matches 100% with SEQ ID NO.1 which encodes a polypeptide (with SEQ ID NO:2) which matches 100% with SEQ ID NO:4, and fragments corresponding to the biological activity and "mature" polypeptide corresponding to amino acids 45-501..."

In response, Applicants point out that Powell *et al.* (U.S. Patent 6,319,689 B1) has the same disclosure and same inventors as Chapman *et al.* (European patent application 855,444 A2). Chapman *et al.* was cited by the Examiner as a 35 USC Section 102 reference against claims 11 and 18 in an official action dated 14 August 2000. In that Action, the Examiner stated that the Chapman *et al.* polypeptide and Applicants' SEQ ID NO:4 are 99.9 percent identical. Applicants responded to this rejection on 19 December 2000, pointing out that the two polypeptides differ by an amino acid at position 130; Applicants' beta-secretase polypeptide has a valine at position 130, while Chapman *et al.*'s polypeptide

has a glutamic acid at this position. Applicants further pointed out that Chapman *et al.* teach only one fragment of their polypeptide, a fragment that starts at position 58 and extends well beyond the carboxyl terminal of Applicants' beta-secretase polypeptide. Applicants concluded that Chapman *et al.* could not have rendered Applicants' rejected claims anticipated at the time Applicants' invention was made. The Examiner agreed as he subsequently allowed the now rejected claims in an Advisory Action dated 9 January 2002.

Turning to the current rejection of claims 11-14 over Powell *et al.*, Applicants' maintain their earlier stated position that the Powell *et al.* polypeptide (which is the same as the Chapman *et al.* polypeptide) and Applicants' claimed polypeptide are not identical. As the Examiner is aware, a proper 102 reference must teach every element of the claimed invention. Applicants' SEQ ID NO:4 differs from the Powell *et al.* polypeptide at amino acid position 130, as discussed above. In addition, Applicants' SEQ ID NOs: 5 and 6 are directed to mouse and rat beta-secretase polypeptides, respectively. These polypeptides differ from Applicants' human beta secretase as shown in the attached sequence comparison labeled as Exhibit A. Thus, Powell *et al.* cannot be considered to have anticipated Applicants' polypeptides of SEQ ID NOs 4, 5, 6, or of the DNAs encoding these polypeptides. Finally, Powell *et al.* does not teach the specific beta-secretase polypeptide fragments embodied in Applicants' claim 14 , and thus this reference cannot be said to have anticipated claim 14.

In view of the foregoing, Applicants respectfully submit that the rejection of claims 11-14 under 35 USC, Section 102(e) is improper and cannot stand. Applicants thus request reconsideration and removal of this rejection.

Rejection Under 35 USC, Section 103(a)

Claim 19 has been rejected under 35 USC, Section 103(a) as allegedly obvious over Powell *et al.* Without conceding in any way to the merits of this rejection, Applicants have canceled claim 19 herein without prejudice. As such, Applicants submit that this rejection is rendered moot, and respectfully request reconsideration and removal of this rejection.

Applicants believe that the claims as presented herein are in condition for allowance, and a notice to that effect is respectfully solicited.

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The Commissioner is hereby authorized to charge any fees which may be required by the accompanying papers, or to credit any overpayment to Deposit Account No. 01-0519.

Respectfully submitted,

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Date: October 22, 2002

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Thousand Oaks, California 91320-1799

MARK UP OF CHANGES MADE TO CLAIMS

11. (thrice amended) An isolated biologically active beta-secretase polypeptide selected
from the group consisting of:

a) the polypeptide of any of SEQ ID NOs: 4, 5, and 6;

b) a fragment of any of SEQ ID NOs. 4, 5, and 6;

c) a polypeptide having one to fifty conservative amino acid changes as compared with the
polypeptide of SEQ ID NO: 4; and

d) the polypeptide encoded by the DNA vector insert of ATCC Deposit Nos. 207158 and
207159.

12. (four times amended) An isolated biologically active beta-secretase polypeptide
encoded by a nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule as set forth in any of SEQ ID Nos:1, 2, and 3;

b) a nucleic acid molecule encoding the polypeptide of any of SEQ ID NOs: 4, 5, and 6;

c) fragments of SEQ ID NOs: 1, 2, and 3:

d) a nucleic acid molecule of the DNA vector insert in ATCC deposit No. 207158;

e) a nucleic acid molecule of the DNA vector insert in ATCC deposit No. 207159; and

f) a nucleic acid molecule having one to fifty conservative amino acid substitutions as compared
with the polypeptide of SEQ ID NO:4.

EXHIBIT A
Beta-Secretase: human vs rat

```
                        *         20         *         40
BACE_human : MAQALPWLLLWMGAGVLPAHGTQHGIRLPLRSGLGGAPLG :  40
BACE_rat   : MAPALRWLLLWVGSGMLPAQGTHLGIRLPLRSGLAGPPLG :  40
             MA AL WLLLW G G LPA GT  GIRLPLRSGL G PLG


                        *         60         *         80
BACE_human : LRLPRETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMT :  80
BACE_rat   : LRLPRETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMT :  80
             LRLPRETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMT


                        *         100        *         120
BACE_human : VGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSST : 120
BACE_rat   : VGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSST : 120
             VGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSST


                        *         140        *         160
BACE_human : YRDLRKGVYVPYTQGKWEGELGTDLVSIPHGPNVTVRANI : 160
BACE_rat   : YRDLRKSVYVPYTQGKWEGELGTDLVSIPHGPNVTVRANI : 160
             YRDLRK VYVPYTQGKWEGELGTDLVSIPHGPNVTVRANI


                        *         180        *         200
BACE_human : AAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDS : 200
BACE_rat   : AAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDS : 200
             AAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDS


                        *         220        *         240
BACE_human : LVKQTHVPNLFSLQLCGAGFPLNQSEVLASVGGSMIIGGI : 240
BACE_rat   : LVKQTHIPNIFSLQLCGAGFPLNQTEALASVGGSMIIGGI : 240
             LVKQTH PN FSLQLCGAGFPLNQ E LASVGGSMIIGGI


                        *         260        *         280
BACE_human : DHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKE : 280
BACE_rat   : DHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKE : 280
             DHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKE


                        *         300        *         320
BACE_human : YNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPD : 320
BACE_rat   : YNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPD : 320
             YNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPD


                        *         340        *         360
BACE_human : GFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRIT : 360
BACE_rat   : GFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRIT : 360
```

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                          GFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRIT

                                  *         380         *         400
BACE_human  :  ILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIME  :  400
BACE_rat    :  ILPQQYLRPVEDVATSQDDCYKFAVSQSSTGTVMGAVIME  :  400
               ILPQQYLRPVEDVATSQDDCYKFA SQSSTGTVMGAVIME


                                  *         420         *         440
BACE_human  :  GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDM  :  440
BACE_rat    :  GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTADM  :  440
               GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVT DM


                                  *         460         *         480
BACE_human  :  EDCGYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQW  :  480
BACE_rat    :  EDCGYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQW  :  480
               EDCGYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQW


                                  *         500
BACE_human  :  RCLRCLRQQHDDFADDISLLK  :  501
BACE_rat    :  RCLRCLRHQHDDFADDISLLK  :  501
               RCLRCLR QHDDFADDISLLK
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Beta-Secretase: human vs mouse

```
                 *        20        *        40
BACE_human : MAQALPWLLLWMGAGVLPAHGTQHGIRLPLRSGLGGAPLG : 40
BACE_mouse : MAPALHWLLLWVGSGMLPAQGTHLGIRLPLRSGLAGPPLG : 40
             MA AL WLLLW G G LPA GT   GIRLPLRSGL G PLG


                 *        60        *        80
BACE_human : LRLPRETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMT : 80
BACE_mouse : LRLPRETDEESEEPGRRGSFVEMVDNLRGKSGQGYYVEMT : 80
             LRLPRETDEE EEPGRRGSFVEMVDNLRGKSGQGYYVEMT


                 *        100       *        120
BACE_human : VGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSST : 120
BACE_mouse : VGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSST : 120
             VGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSST


                 *        140       *        160
BACE_human : YRDLRKGVYVPYTQGKWEGELGTDLVSIPHGPNVTVRANI : 160
BACE_mouse : YRDLRKGVYVPYTQGKWEGELGTDLVSIPHGPNVTVRANI : 160
             YRDLRKGVYVPYTQGKWEGELGTDLVSIPHGPNVTVRANI


                 *        180       *        200
BACE_human : AAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDS : 200
BACE_mouse : AAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDS : 200
             AAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDS


                 *        220       *        240
BACE_human : LVKQTHVPNLFSLQLCGAGFPLNQSEVLASVGGSMIIGGI : 240
BACE_mouse : LVKQTHIPNIFSLQLCGAGFPLNQTEALASVGGSMIIGGI : 240
             LVKQTH PN FSLQLCGAGFPLNQ E LASVGGSMIIGGI


                 *        260       *        280
BACE_human : DHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKE : 280
BACE_mouse : DHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKE : 280
             DHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKE


                 *        300       *        320
BACE_human : YNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPD : 320
BACE_mouse : YNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPD : 320
             YNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAASSTEKFPD


                 *        340       *        360
BACE_human : GFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRIT : 360
BACE_mouse : GFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRIT : 360
             GFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRIT
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                       *          380         *          400
BACE_human : ILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIME : 400
BACE_mouse : ILPQQYLRPVEDVATSQDDCYKFAVSQSSTGTVMGAVIME : 400
             ILPQQYLRPVEDVATSQDDCYKFA SQSSTGTVMGAVIME


                       *          420         *          440
BACE_human : GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDM : 440
BACE_mouse : GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTADM : 440
             GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVT DM


                       *          460         *          480
BACE_human : EDCGYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQW : 480
BACE_mouse : EDCGYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQW : 480
             EDCGYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQW


                       *          500
BACE_human : RCLRCLRQQHDDFADDISLLK : 501
BACE_mouse : RCLRCLRHQHDDFADDISLLK : 501
             RCLRCLR QHDDFADDISLLK
```

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